CONDENSATION OF NITROPARAFFINS WITH β-SUBSTITUTED ACRYLATES LEADING TO THE SYNTHESIS OF 1-SUBSTITUTED PYRROLIZIDINES

BY

DONALD LOUIS FELLEY

B.S., Arkansas State College, 1941
M.S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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Introduction

The most convenient method for the synthesis of pyrrolizidine and certain substituted pyrrolizidines is the reductive cyclization over copper chromite catalyst of γ-nitropimelic esters, introduced by Leonard.[1]

A logical extension of this work would be the condensation of nitroparaffins, particularly nitromethane, with β-substituted acrylic esters to yield β-substituted-γ-nitrobutyric esters, which on further condensation with acrylic esters, followed by reductive cyclization, should lead to 1-substituted pyrrolizidines. Accordingly, this research was directed toward a study of the conditions necessary to effect these condensations and reductions, and studies on certain of the 1-substituted pyrrolizidines which might result, which form nuclei for several families of alkaloids. It was further desired to investigate the possibility of extending the method to the synthesis of larger heterocyclic systems, by replacing the β-substituted acrylic esters with esters of cyclopropanecarboxylic acids and sorbic acid.

Discussion Of Results

The condensation of nitromethane with ethyl crotonate was found to be a practical means of initiating the synthesis of 1-methylpyrrolizidine.[2] A study of the conditions for this reaction indicated that benzyltrimethylammonium butoxide was the most effective catalyst, and, of a number of amines studied, that diisopropylamine was the most effective. The ethyl β-methyl-γ-nitrobutyrate resulting from this condensation was caused to react with ethyl acrylate in the presence

of benzyltrimethylammonium hydroxide to yield dimethyl β-methyl-γ-nitropimelate, which gave 1-methylpyrrolizidine on reductive cyclization. Through an analogous series of reactions, starting with diethyl ethylidenemalonate in place of ethyl crotonate, 1-methylpyrrolizidine was synthesized in poorer yield. This base can exist in two racemic diastereoisomeric forms, both of which have been isolated from alkaloids in their active forms, known as *l*-heliotridane and *l*-pseudoheliotridane. The synthetic bases from both of the above preparations were separated into two diastereoisomeric racemates, both by fractional distillation and by chromatographic adsorption on alumina. The isomer present in larger amount was resolved through the bi-*d*-tartrate, and the active amine thus obtained was shown, by optical rotation, infrared absorption spectra and melting points of derivatives, to be *d*-pseudoheliotridane. This evidence indicates that previous workers who had synthesized 1-methylpyrrolizidine,[3] had also obtained predominantly *dl*-pseudoheliotridane, rather than *dl*-heliotridane, as they had suspected.

In attempting to synthesize 1-hydroxymethylpyrrolizidine (isoretronecanol, trachelantamidine), the condensation of nitromethane or methyl γ-nitrobutyrate with dimethyl fumarate in the presence of amines was shown to give largely unsaturated esters and higher condensation products, as had been previously reported.[4] The use of ethyl γ-acetoxycrotonate as the β-substituted acrylate led to the synthesis of diethyl β-acetoxymethyl-γ-nitropimelate, which on reductive cyclization at 265° gave only 1-methylpyrrolizidine, due to hydrogenolysis of the 1,3-aminoalcohol linkage resulting. Hydrogenation at a lower temperature gave mostly a mixture of incompletely reduced products, plus a small amount of distillable oil. This oil when subjected to purification by chromatography, gave a small amount of picrate which corresponded in melting point to *l*-trachelantamidine picrate, and is therefore probably *dl*-trachelantamidine picrate. In view of the complications involved in the reduction step, this type of reductive cyclization does not appear to be a practical approach to the

synthesis of 1-hydroxymethylpyrrolizidine.

The condensation of nitromethane with ethyl cinnamate was carried out to give ethyl β-phenyl-γ-nitrobutyrate, which gave 1-ethyl-3-phenylpyrrolidine on hydrogenation. Further condensation of this nitroester with ethyl acrylate, in an attempted synthesis of 1-phenylpyrrolizidine gave an intractable oil, which gave no identifiable product on hydrogenation.

The addition of both nitromethane and methyl γ-nitrobutyrate to methyl sorbate, in the presence of diisopropylamine, was effected. Reductive cyclization of the adducts gave, in the former case, no identifiable product, and in the latter case, a tertiary amine which was neither 1-*n*-propylpyrrolizidine or 6-methyl-1-azabicyclo[5,3,0]decane, depending on whether the original addition proceeded in a 1,4- or a 1,6-fashion. The structure proof of this product is in progress at present.

Attempted condensations of nitromethane with ethyl cyclopropanecarboxylate, diethyl cyclopropane-1,1-dicarboxylate, or acetocyclopropane in the presence of a number of basic catalysts did not proceed. Use of these cyclopropane derivatives as a route to nitrogen heterocyclic molecules containing six-membered rings does not appear to be feasible under the conditions studied.

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VITA

The author was born in Memphis, Tennessee on February 7, 1921. He graduated from high school in May, 1937, and received the Bachelor of Science degree from Arkansas State College in May, 1941. He attended the University of Arkansas in the summer of 1941, and was employed as a government inspector of powder and explosives from August, 1941 to April, 1942. From April, 1942 to April, 1946, he was a member of the United States Army. He entered the Graduate College of the University of Illinois in June, 1946, and received the degree of Master of Science in August, 1947. He held a teaching assistantship from September, 1947 to August, 1948, and a University Fellowship from September, 1948 to June, 1949.

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